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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,646	08/02/2001	Shinichi Ayabe	JKM-001	5225

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EXAMINER	
KALLIS, RUSSELL	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,646	AYABE ET AL.	
	Examiner	Art Unit	
	Russell Kallis	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,39 and 48-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,39,47-51,55-63 and 65-68* is/are rejected.

7)☒ Claim(s) *52-54 and 64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 August 2001 and 20 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/09/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *attached sequence report*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/20/2004 has been entered.

Claims 35, 39, 47-67 and 68 are pending and examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The added claimed material which is not supported by the original disclosure is as follows: Newly added Claims 61-63 recite homology (sequence identity) of 80%, 90% and 95% to nucleotides 144 to 1712 of SEQ ID NO: 1, while the specification only supports homology for the nucleotides 144 to 1712 of SEQ ID NO: 1 of 70%. Further, the specification only supports homology (sequence identity) of 80%, 90% and 95% to the full length of SEQ ID NO: 1 on page

of the specification. Thus, the claims are drawn to NEW MATTER. Applicant is invited to point to the page and line number in the specification where support can be found. Absent of such support, Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 35, 39, 47-51, 55-63 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to an isolated polynucleotide that encodes SEQ ID NO: 2, or a polynucleotide complementary thereto, or a variant of SEQ ID NO: 2 that catalyzes the synthesis of 2-hydroxyisoflavanone from flavanone wherein the variant comprises any protein that catalyzes the synthesis of 2-hydroxyisoflavanone from flavanone; or a protein having anywhere from 1 to 20 substitutions, deletions or additions to SEQ ID NO: 2; or 1 to 20 substitutions of any amino acid to SEQ ID NO: 2; or 1 to 20 substitutions to SEQ ID NO: 2 selected from the group consisting of between any one of Ala,Val, Leu and Ile, between Ser and Thr, between Asp and Glu, between Asn and Gln, between Lys and Arg and between Phe and Tyr; or a polynucleotide complementary thereto; and an isolated polynucleotide encoding a 2-hydroxyisoflavanone synthase having at least 70% sequence identity to nucleotides 144-1712 of SEQ ID NO: 1 or a complement of said nucleic acid sequence; and a method of producing 2-hydroxyisoflavanone synthase in a host cell.

Applicants describe SEQ ID NO: 1 encoding a 2-hydroxyisoflavanone synthase of SEQ ID NO: 2 from licorice.

Applicants do not describe any polynucleotides complementary to a polynucleotide encoding SEQ ID NO: 2 other than the polynucleotide sequence complementary to SEQ ID NO: 1, or variants of SEQ ID NO: 2 encoding a 2-hydroxyisoflavanone synthase or polynucleotides having at least 70% sequence identity to SEQ ID NO: 1 and encoding a 2-hydroxyisoflavanone synthase other than SEQ ID NO: 1 encoding SEQ ID NO: 2.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. The court stated that, "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of sequences that are complementary to the polynucleotide encoding SEQ ID NO: 2, or that are 70% homologous to SEQ ID NO: 1; or have 1 to 20 substitutions, additions or deletions to SEQ ID NO: 2, or are variant of SEQ ID NO: 2 and have 2-hydroxyisoflavanone activity. Applicants only describe SEQ ID NO: 1 encoding a 2-hydroxyisoflavanone synthase of SEQ ID NO: 2 from licorice and the sequence complementary to SEQ ID NO: 1. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of variants of SEQ ID NO: 2 that catalyze the synthesis of 2-hydroxyisoflavanone from flavanone or that have at least 70% sequence identity to SEQ ID NO: 1 and encode a 2-hydroxyisoflavanone synthase. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of

description of the necessary elements essential for 2-hydroxyisoflavanone synthase activity, it remains unclear what features identify a 2-hydroxyisoflavanone synthase. Since the genus of polynucleotides encoding the variants of SEQ ID NO: 2 that catalyze the synthesis of 2-hydroxyisoflavanone from flavanone or that have at least 70% sequence identity to SEQ ID NO: 1 and encode a 2-hydroxyisoflavanone synthase has not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims.

Sequences that are 70% homologous to SEQ ID NO: 1, or have 1 to 20 substitutions, additions, or deletions to SEQ ID NO: 2, or are variant of SEQ ID NO: 2, or have 1 to 20 substitutions to SEQ ID NO: 2 comprising any one of Ala,Val, Leu and Ile, between Ser and Thr, between Asp and Glu, between Asn and Gln, between Lys and Arg and between Phe and Tyr and have 2-hydroxyisoflavanone activity encompass naturally occurring allelic variants, mutants of the 2-hydroxyisoflavanone synthase of SEQ ID NO: 2, as well as sequences encoding proteins having no known 2-hydroxyisoflavanone synthase activity, of which Applicant is not in possession. Accordingly, the specification fails to provide an adequate written description to support the genus of 2-hydroxyisoflavanone synthase encoding polynucleotides or 2-hydroxyisoflavanone synthase polypeptide variants encompassed by percent identity or the variant language as set forth in the claims, or their complementary sequence as broadly claimed. (See Written Description guidelines published in Federal Register/Vol. 66, No.4/Friday, January 5, 2001/Notices: p.1099-1111).

Claims 35, 39, 47-51, 55-63 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims drawn to the isolated polynucleotide of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2 having 2-hydroxyisoflavanone activity and a method for producing 2-hydroxyisoflavanone synthase of SEQ ID NO: 2 by culturing a cell transformed with SEQ ID NO: 1, does not reasonably provide enablement for claims drawn to non-exemplified variants of SEQ ID NO: 2 that catalyze the synthesis of 2-hydroxyisoflavanone from flavanone; wherein the variant comprises any non-exemplified protein that catalyzes the synthesis of 2-hydroxyisoflavanone from flavanone; or a non-exemplified protein having anywhere from 1 to 20 substitutions, deletions or additions to SEQ ID NO: 2; or 1 to 20 substitutions of any amino acid to SEQ ID NO: 2; or 1 to 20 substitutions to SEQ ID NO: 2 selected from the group consisting of between any one of Ala,Val, Leu and Ile, between Ser and Thr, between Asp and Glu, between Asn and Gln, between Lys and Arg and between Phe and Tyr; or for a polynucleotide complementary thereto; and non-exemplified polynucleotides encoding a 2-hydroxyisoflavanone synthase having at least 70% sequence identity to nucleotides 144-1712 of SEQ ID NO: 1 or a complement of said nucleic acid sequence, or a polynucleotide complemntary thereto; and a method of producing a non-exemplified 2-hydroxyisoflavanone synthase in a host cell using any non-exemplified 2-hydroxyisoflavanone synthase coding sequence other than SEQ ID NO: 1 encoding SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are broadly drawn to an isolated polynucleotide that encodes SEQ ID NO: 2, or a polynucleotide complementary thereto, or a variant of SEQ ID NO: 2 that catalyzes the synthesis of 2-hydroxyisoflavanone from flavanone wherein the variant comprises any protein that catalyzes the synthesis of 2-hydroxyisoflavanone from flavanone; or a protein having anywhere from 1 to 20 substitutions, deletions or additions to SEQ ID NO: 2; or 1 to 20 substitutions of any amino acid to SEQ ID NO: 2; or 1 to 20 substitutions to SEQ ID NO: 2 selected from the group consisting of between any one of Ala,Val, Leu and Ile, between Ser and Thr, between Asp and Glu, between Asn and Gln, between Lys and Arg and between Phe and Tyr; or a polynucleotide complementary thereto; and an isolated polynucleotide encoding a 2-hydroxyisoflavanone synthase having at least 70% sequence identity to nucleotides 144-1712 of SEQ ID NO: 1 or a complement of said nucleic acid sequence; and a method of producing 2-hydroxyisoflavanone synthase in a host cell.

Applicants teach isolation of cDNA encoding a 2-hydroxyisoflavanone synthase from licorice cells treated with a fungal elicitor consisting of yeast extract and TLC analysis of product formation of a recombinant 2-hydroxyisoflavanone synthase isolated from a yeast expression system (specification pages 23-29) and transformation of tobacco with a sense cDNA encoding a 2-hydroxyisoflavanone synthase from licorice (specification pages 31-37).

Applicants do not teach the isolation or synthesis of other polynucleotides that encode a 2-hydroxyisoflavanone synthase encompassed by the claims. Applicants fail to teach which amino acids can be deleted, substituted or added and still produce a protein with the same function as the protein encoded by SEQ ID NO: 2 or a variant of SEQ ID NO: 2 that catalyzes the synthesis of 2-hydroxyisoflavanone from flavanone; or polynucleotides that have at least 70% sequence identity with SEQ ID NO: 2 and have 2-hydroxyisoflavanone synthase.

The state of the art for making additions, substitutions or deletions to a protein with the intent of recovering a protein having the same activity is unpredictably and is illustrated in an example where a small number of changes to the coding region for a strict desaturase resulted in an enzyme with a hydroxylase activity showing that a small number of changes to the coding region of a desaturase could account for the functional divergence seen across a range of enzymes involved in fatty acid metabolism (Broun P. *et al.* Science Vol. 282; 13 November 1998, pp. 1315-1317; Abstract lines 4-6 and p. 1317 column 1, lines 37-56).

The state of the art for isolating and deducing cytochrome P450 enzymatic activity from structure alone is also unpredictable because of the limited knowledge of enzymatic activity for cytochrome P450 subfamily members available in the art. For example, the isolation from Medicago truncatula of cDNA classified as P450 81E subfamily members showed a common

affinity for the same substrate but produced different products when expressed in yeast. (Liu C. *et al.* The Plant Journal, 2003; Vol. 36 pp. 471-484; see abstract and page 473 column 2, the entire column). The results of Liu are closely paralleled in the results of a mutagenesis analysis of amino acid residues of a CYP93C2 poylpeptide from soybean that are required for catalytic activity that synthesizes 2-hydroxyisoflavanone from flavanone. A substitution of a Threonine for a Serine at position 310 resulted in a significant shift to a 3-hydroxyisoflavanone product and a Lysine substituted for a Threonine at position 375 completely eliminated production of the isoflavonoid (Sawada Y. *et al.* The Plant Journal, 2002; Vol. 31 No. 5; pp. 555-564; see abstract).

Given the lack of guidance in the instant specification, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified polynucleotide sequences encoding putative variant polypeptides of SEQ ID NO: 2 having substitutions, additions or deletions of 1 to 20 amino acids or substitutions selected from the group consisting of between any one of Ala,Val, Leu and Ile, between Ser and Thr, between Asp and Glu, between Asn and Gln, between Lys and Arg and between Phe and Tyr; or a polynucleotide complementary thereto; or non-exemplified polynucleotide sequences having at least 70% sequence identity to the coding region of SEQ ID NO: 1 that also catalyze the synthesis of 2-hydroxyisoflavanone from flavanone, by producing expression vectors and testing for activity and 2-hydroxyisoflavanone product formation from flavanone, in order to identify those polynucleotides that when expressed in a host cell produce 2-hydroxyisoflavanone synthase.

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled throughout the broad scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35, 47-50, 60, 65 and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Siminszky, B. *et al.* GenBank Accession AF022462 made public on January 2, 1998.

The claims are broadly drawn to a polynucleotide complementary to the polynucleotide encoding SEQ ID NO: 2; wherein the office interprets "a polynucleotide complementary thereto" as a polynucleotide of any length that is also complementary to any polynucleotide comprised within a polynucleotide sequence that encodes SEQ ID NO: 2.

Siminszky teaches a cytochrome P450 polynucleotide sequence that has a sequence that is complementary to SEQ ID NO: 1 over nucleotides 439-466 of SEQ ID NO: 1; and an expression vector that expresses the sequence in a sense direction, and thus the reference teaches all the limitations of Claims 35, 47-50, 60, 65 and 67. Amending the rejected claims to recite "the polynucleotide complementary thereto" would obviate this rejection.

Claims 35, 39, 47-51, 55-63 and 65-68 are rejected.

Claims 52-54 and 64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 39, 51-59, 61-64, 66 and 68 are deemed free of the prior art given the failure of the prior art to teach or suggest a polynucleotide of SEQ ID NO: 1 encoding a 2-hydroxyisoflavanone synthase of SEQ ID NO: 2 and a method of culturing a host cell transformed with SEQ ID NO: 1 to produce a 2-hydroxyisoflavanone synthase of SEQ ID NO: 2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Kallis

Russell Kallis Ph.D.
December 17, 2004